

FESCUE TOXICOSIS IN HORSES

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1. INTRODUCTION

For years veterinarians and horse owners reported reproductive problems in mares that consume tall fescue (Garrett et al., 1980; Villahoz et al., 1984; Poppenga et al., 1984). Bacon et al. (1977) reported the first conclusive evidence of the presence of an endophytic fungus in tall fescue that was later identified as *Neotyphodium coenophialum*. The first controlled study with gravid mares grazing either endophyte-free (E-) or endophyte-infected (E+) pastures was conducted by Monroe et al., 1988. In this study, increased gestation lengths, agalactia, foal and mare mortality, tough and thickened placentas, weak and dysmature foals, and reduced serum prolactin and progesterone levels occurred in mares consuming (E+) pasture, whereas horses on (E-) pasture appeared normal (Figure 1).

A symbiotic relationship exists between the endophyte and the plant. Infected grass is more resistant to overgrazing, insect damage, and drought stress (Ball et al., 1987). The endophytic fungus is only transmitted by seed to new seedlings. New fungus-free varieties have been developed, but lack of vigor and stand persistence have made them unpopular in many regions of the United States.

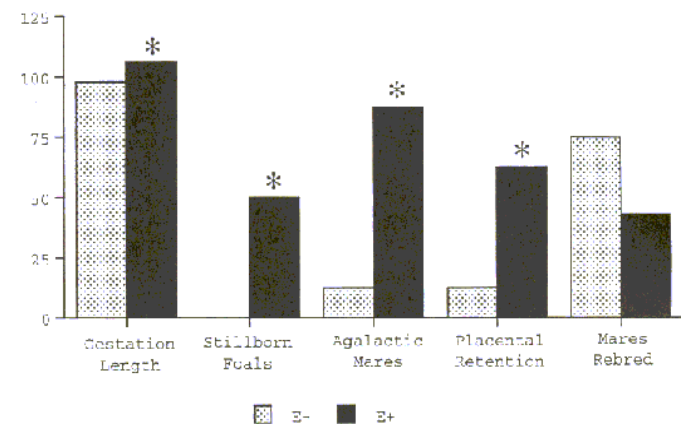


Figure 1. Effect of endophyte-infected fescue on gestation length foal mortality, agalactia, incidence of placental retention, and rebreeding response in mares (adapted from Monroe et al., 1988). Stars indicate difference between treatments ($P < .05$).

2. CLINICAL SIGNS OF *NEOTYPHODIUM* TOXICOSIS IN HORSES

2.1. Gravid Mares

2.1.1. Increased Length of Gestation. Gestation length of mares increased 27 days when consuming endophyte-infected (E+) fescue grass, compared to mares consuming endophyte-free (E-) grass (Monroe et al., 1988). Putnam et al. (1991), Earle et al. (1990), and Redmond et al. (1994) observed similar results. Severe dystocia is a frequent observation in mares who try to foal after the extended gestation period. Supplementing E- and E+ mares on pastures with 50% of their N.R.C. requirements for energy by using whole shelled corn

provided no beneficial effects on length of gestation or dystocia. In this study, 66% of the E+ mares with energy supplementation exhibited prolonged length of gestation and died due to dystocia, while 50% of the E+ mares without supplementation exhibited prolonged length of gestation and death due to dystocia. Putnam et al. (1991) reported 10 of 11 mares on E+ fescue experienced obvious clinical dystocia, and only one foal survived the natal period.

The dystocia seems to be a result of inadequate preparation of the reproductive tract for foaling, prolonged gestation and fetal malpresentation. Due to prolonged gestation, foals usually have larger than normal skeletal frames, increasing the difficulty of expelling a fetus through an unprepared tract (Monroe et al., 1988; Putnam et al., 1991; Redmond et al., 1991a). Additionally, foals are often rotated 90 to 180 degrees from the normal position for delivery (Taylor et al., 1985; Monroe et al., 1988; Redmond et al., 1991a). The failure of the mare, or the foal, to initiate the events that prepare for and result in normal parturition results in the subsequent catastrophic events of dystocia, as well as mare and foal mortality in many instances.

2.1.2. Agalactia. The effects of endophyte consumption on milk production depend on the species of animal in question. Cattle (Strahan et al., 1987; Porter and Thompson, 1992; Schmidt and Osborn, 1993), sheep (Stidham et al., 1982), and mice (Zavos et al., 1988) have been shown to have reduced milk yields, whereas horses (Monroe et al., 1988; Figure 2) and rabbits (Daniels et al., 1984) exhibit reduced milk yields or complete agalactia. The connection between tall fescue toxicosis and lactogenesis seems to be through the effects of the ergot alkaloids on lactogenic hormones. Cattle, sheep, and mice have both placental lactogen and prolactin (Forsyth, 1986). In contrast, horses and rabbits rely on prolactin to stimulate parturition lactogenesis (Forsyth, 1986). The depressive effects of ergot alkaloids on prolactin secretion may suppress prolactin's effect on lactogenesis in cattle, sheep, and mice, but have no effect on placental lactogen. As a result, the placental lactogen and the small level of pituitary prolactin may be sufficient to initiate parturition lactogenesis. In the horse, it seems that the reduced prolactin secretion from the pituitary lactotrophic cells results in agalactia. Apparently, the alkaloids of tall fescue are serving as D2 dopamine receptor agonists at the pituitary level (Strickland et al., 1992). Also, unlike ruminants, the horse does not benefit from pre-gastric metabolism of alkaloids and would be subject to larger doses of the alkaloids from E+ tall fescue (Wachenheim et al., 1992).

Eighty-eight percent of E+ mares were agalactia when maintained on fescue up to foaling (Monroe et al., 1988; Figure 1). The milk of agalactia mares often appears as a brown or straw-colored oily-looking fluid, rather than the white milk of normal mares. This fluid has little nutritional

value and foals invariably die unless bottle-fed. Another frequent complication affecting foal viability is the lack of normal immunoglobulins in the mare's milk. There is a lack of normal immunoglobulins in foals from mares that have the straw colored fluid rather than white milk (Kouba et al., 1995). Also, there is a frequent lack of transfer of passive immunity from mares with normal looking white milk but low level milk production.

2.1.3. Thickened, Reddish Colored Placentas. The placentas of mares grazing E+ tall fescue are thickened, reddish colored, and heavier with an increased retention than for E- mares (Monroe et al., 1988). Using an Ingstrom meter to measure stress and strain, these E+ placentas appeared to be more resistant to forces that would tear them which partially explains why some foals are unable to break through the thickened placentas (Monroe et al. 1988). Taylor et al. (1985) reported heavier and thicker placentas from many mares consuming E+ seed than from mares consuming E- seed. DNA, RNA, and collagen content were greater in the placentas of mares consuming E+ seed. Caudle and Miller (1990) reported placental edema, placentitis and mineralization of placentas from mares grazing E+ pastures. Brendemuehl et al. (1994) grazed mares on E+ fescue either continuously, from 300 days of gestation to foaling, from gestation day 60 to 300, or no exposure to fescue at all. They observed an increase in weight and width of the combined chorioallantois from mares exposed to E+ fescue continuously or from day 300 to foaling. Brendemuehl (1994) reported increased placental thickness in E+ mares immediately before parturition. Using 12 E+ and 12 E- mares, increased placental thickness was observed in one E+ mare, 32 hours prior to parturition, with 10 of the other mares demonstrating an increase in thickness a mean of 6.5 hours prior to the onset of parturition. An elective Cesarean section was performed on one E+ mare at 358 days of gestation and within two hours of noting an increase in placental thickening. At surgery, the placenta was reported to be thickened in a plaque-like fashion in an area of the ventral portion of the gravid horn. The thickened portion of the chorioallantois was noted to be separated from the uterus. It was felt that this could be an explanation for the premature presentation of the chorioallantois commonly called "red bagging" in the equine industry.

2.1.4. Foal Vigor and Viability. Monroe et al., (1988) observed large-framed, dysmature and emaciated looking (poor muscle mass) foals with overgrown hooves in E+ mares whose foals survived the birthing process and whose average gestation length was 27 days past the expected foaling date (figures 1 and 2). These foals appeared weak and many times exhibited a "dummy-like" behavior. Later, with proper care, the foals appeared normal (Monroe et al., 1988; Earle et al., 1990). Septicemia is a frequent problem and is likely a result of the low level of passive immunity. Putnam et al. (1991) reported that of 11 mares grazing E+ fescue, only three foals were alive at birth, and only one of the three survived the first month of life. Dysmaturity or neonatal death of foals was not observed in 11 mares grazing E- pastures.

Taylor et al. (1985) and Kosauke et al. (1989) observed lack of lung maturation in stillborn foals born to E+ mares. Amniotic fluid from E+ mares lacked pulmonary phospholipids and phosphatidylethanolamine was present in only 12% of E+ mares (Clare et al., 1994). These data suggest that lack of lung maturation may be a contributing factor to the high rate of foal death observed in E+ mares. Boosinger et al. (1994) examined several organs and tissue from foals of E+ and E- mares. Histologic studies of thyroid glands from foals exposed to E+ continuously or after gestation day 300 revealed numerous distended colloid filled thyroid follicles lined by flattened cuboidal epithelial cells. Mean plasma T₃ concentrations were reduced in these foals. Foals from mares exposed to E+ continuously or from day 300 to foaling demonstrated a response to thyroid stimulating hormone (TSH) by showing improved mental alertness, desire to stand, and good suckle reflex.

Brendemuehl (1995) collected colostrum from normal mares and tested it for IgG concentration. Foals from mares exposed to E+ fescue continuously or from gestation day 300 were administered 11 of the pooled colostrum by nasogastric tube within one hour of birth. Compared to control foals, these foals had decreased serum IgG concentrations. These data combined with other data suggest that foals from E+ mares receive less IgGs from the mare's milk and absorption rate is lower even if the milk IgG levels are at or near normal levels. These factors, combined with the lower level of colostrum production in E+ mares clearly explain why many foals from E+ mares quickly become septic. And along with the low nutrient intake from milk probably account for many foal deaths in E+ mares with live foals at birth.

Brendemuehl et al. (1994) observed lower serum T₃, ACTH, cortisol and total progestogen levels in foals from E+ mares compared to foals from E- mares.

2.1.5. Body Temperature, Blood Flow and Laminitis. In cattle and sheep, blood flow to the peripheral tissues decreased and body temperature increased when tall fescue seed was included in the diet (Rhodes et al., 1991). The reduction in blood flow to the peripheral tissues is likely related to increased body temperature because the animal is less efficient in cooling itself. Unlike cattle and sheep, pregnant mares exhibit no increase in body temperature when exposed to the endophytic toxins (Monroe et al., 1988; Putnam et al., 1991). However, horses sweat more freely than cattle and are more capable of cooling themselves. Putnam et al. (1991) observed increased sweating in gravid mares grazing E+ tall fescue.

In cattle, it seems that peripheral vasoconstriction caused by the alkaloids of E+ tall fescue is related to "fescue foot" (Solomons et al., 1989). Rorhback et al. (1995) reviewed data from 185,781 horses of which 5,536 had a diagnosis of laminitis. Although these data are preliminary, they concluded that there appeared to be a relationship between laminitis in horses and consumption of E+ fescue grass. Abney et al. (1993) observed a vasoconstrictive effect of ergot alkaloids on equine vessels *in vitro*. Carbohydrate overload (Gemer et al., 1975) and aqueous extract of black walnut (Galey et al., 1990) are associated with the development of

laminitis in horses. The aqueous extract of black walnut caused post capillary vasoconstriction, increased capillary hydrostatic pressure, and transvascular fluid movement, resulting in increased tissue pressure, edema, vascular collapse, and ischemia in the equine digit (Eaton et al., 1995). It is possible that through interaction of the ergot alkaloids with the adrenergic receptors of the sympathetic nervous system, similar responses may be occurring in horses consuming E+ fescue. Direct evidence for this theory does not exist.

2.1.6. Mare Abortions and Fertility. Abortions in mares occur after rapid separations of the placenta from the endometrium. Of 1211 abortion/stillbirths presented to a diagnostic laboratory in Kentucky (USA), placentitis and dystocia were the commonly diagnosed causes (approximately 11%, each), with congenital abnormalities (8%), twins (6%), umbilical cord torsion and premature placental edema (4%, each) and Equine Herpes Virus and other bacterial infections (3%, each) being the other diagnostic causes (Pugh, 1996). "Red bagging", or premature placental separations, and stillborn foals are frequently reported by veterinarians in the field for mares grazing E+ fescue. Good quantitative data on the abortion rate of mares past 30 days of gestation does not exist.

Brendemuehl et al., 1994 observed the effects of E+ fescue on mare cyclicity, pregnancy rates and embryonic death rates. Mares grazing E+ pastures demonstrated prolonged luteal functions, decreased per cycle pregnancy rates, and increased early embryonic death rates compared to those grazing E- pastures.

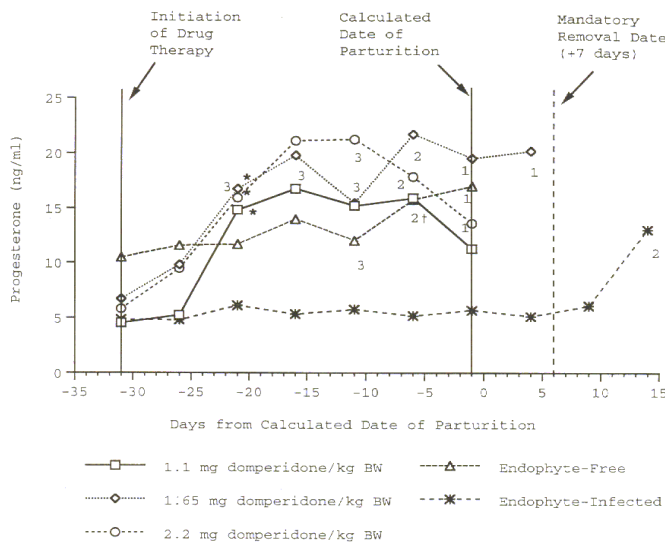


Figure 2. Effect of endophyte-infected fescue and domperidone treatment on serum progesterone levels in gravid mares. First detectable differences ($P < .05$) from pre-treatment levels are indicated by stars. Unless otherwise indicated, data points represent four mares per treatment (dagger indicates number of mares in EF group). Mares which were not prepared for parturition seven days after the calculated date of parturition (as determined by veterinary examination) were relocated to endophyte-free pasture (from Redmond, 1994).

2.2. Growing Horses

Effects on Growth Rate and Digestibility. Consumption of E+ tall fescue or treatment with its extract causes a

reduction in rate of gain and feed intake in cattle (Schmidt et al., 1982; Hoveland et al., 1983; Bond and Bolt, 1986), rats (Neal and Schmidt, 1985), and rabbits (Daniels et al., 1984). No reduction in growth rate was observed in yearling horses when corn-based concentrates were used to supplement E+ or E hay (McCann et al., 1992). Also, Pendergraft and Arns (1993) observed similar gains in yearling horses consuming E+ or E- hay with concentrate supplementation to meet NRC requirements for growth. However, average daily gains were reduced by 57% (.24 and .56 kg for high- and low-endophyte treatments, respectively) in yearling horses grazing E+ pasture without supplementation with a similar reduction in gain for steers in the same study (Aiken et al., 1993).

Redmond et al. (1991b) and McCann et al. (1992) observed lower intake and digestibility for E+ hay fed to mature geldings and yearling horses, respectively. McCann et al. (1993) and Pendergraft and Arns (1993) found no differences in digestibility due to the presence of the endophyte in hay when yearling horses were fed concentrate with hay. Concentrate supplementation was used in both studies to meet NRC requirements for growth for yearling horses.

These results suggest that the effects of endophyte consumption on digestibility and growth rate may be lessened by the inclusion of concentrates in the diet. In contrast, energy supplementation has no beneficial effects for alleviating lactation and reproductive problems in gravid mares that graze E+ pasture (Earle et al., 1990).

2.3. Stallions

Little information exists relative to the effect of E+ on the reproductive system of stallions. However, Thomson et al. (1996) tested the hypothesis that prolactin mediates increases in seminal volumes induced by sexual stimulation in stallions. In one treatment, the effect of bromocriptine on stallion semen and plasma prolactin levels was studied. Bromocriptine is an ergot alkaloid shown to elicit similar effects as E+ fescue. However, bromocriptine is not one of the ergot alkaloids present in E+ fescue grass. Plasma prolactin was decreased by bromocriptine treatment and semen volume after sexual stimulation was also reduced. Volume of gelatinous material, sperm concentration, motility, pH, number of spermatozoa per ejaculate and prolactin concentration in semen were not affected by treatment. Therefore, it is possible that maintaining stallions on E+ pasture during breeding could have an effect on semen volume.

3. ENDOCRINOLOGY OF THE MARE AND FOAL

3.1. Prolactin

One of the most consistent signs of tall fescue toxicosis is decreased serum prolactin levels in animals consuming E+ tall fescue (Neal and Schmidt, 1985; Bond and Bolt, 1986; Elsasser and Bolt, 1987; Earle et al., 1990; Redmond, 1994, Figure 3). For an in-depth study of the control of prolactin secretion in mammals, the reader is referred to a review by Ben-Jonathan et al. (1989). Only a brief explanation of the control of prolactin secretion will be presented herein; however, it is felt that prolactin and dopamine receptors are of

such importance in the equine tall fescue toxicosis malady that they warrant some discussion.

Control of prolactin secretion from lactotrophs of the anterior pituitary is primarily through tonic inhibition by dopamine, produced in the hypothalamus or posterior pituitary (Peters et al., 1981; Ben-Jonathon et al., 1989). Dopamine is transported to the anterior pituitary via the hypothalamic/hypophysial portal system (Guyton, 1986). Dopamine exerts its inhibitory action on prolactin secretion through interaction with the D2 dopamine receptor located on the lactotrophic cell. Interaction with this receptor is thought to activate a pertussis-sensitive G protein (Boyd et al., 1988), which in turn may cause a decrease in C-AMP and calcium concentration in the lactotroph as well as a hyperpolarization of the cell membrane (Ben-Jonathon et al., 1989). Compounds interacting with this receptor as agonists will cause suppression in prolactin secretion.

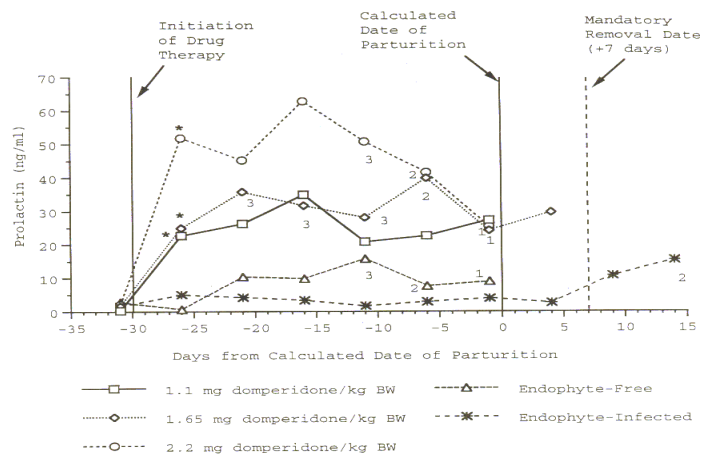


Figure 3. Effect of endophyte-infected fescue and domperidone treatment on serum prolactin levels in gravid mares. First detectable differences ($P < .05$) from pre-treatment levels are indicated by stars. Unless otherwise indicated, data points represent four mares, per treatment. Mares which were not prepared for parturition seven days.

Although primary control of prolactin secretion in mammals is through tonic inhibition, stimulatory mechanisms are also involved in the control of prolactin secretion (Ben-Jonathon et al., 1989). Proposed stimulatory mechanisms include relaxin, oxytocin, bradykinin (as paracrine agent), thyrotropin-releasing hormone, vasoactive intestinal polypeptide, serotonin, and angiotensin II (Ben-Jonathon, 1989; Jones et al., 1989; Sortino, et al., 1989; Mori et al., 1990).

The involvement of prolactin in mammary development and in the initiation of lactation has been well documented (Houdebine et al., 1985). However, prolactin has been reported to have receptors in other tissues as well. These include liver, kidney, cerebral cortex, and seminal vesicles (Turkington and Frantz, 1972). The location of suitable binding sites for prolactin in tissues other than mammary tissue indicates its importance in other processes besides lactation. Prolactin affects the circadian rhythm of lipogenesis and insulin receptor number in hepatic tissue of hamsters (Cincotta and Meier, 1985a, 1989). Prolactin treatment of in vitro hamster hepatocytes increased the lipogenic rate in relation to untreated hepatocytes (Cincotta and Meier, 1989).

Additionally, Cincotta and Meier (1985b) reported that inhibition of prolactin secretion in hamsters decreased hepatic lipogenic rates. Therefore, a reduction in serum prolactin levels in animals receiving a diet of E+ tall fescue may partially explain the reduced body weight gains seen in these animals, should prolactin elicit similar effects on lipogenesis in animals other than hamsters. Additionally, prolactin has been reported to increase feed intake in female rats in a dose-related manner (Gettens et al., 1989). Because reductions in feed intake and serum prolactin are signs of animals grazing E+ tall fescue, it is possible that the lowered serum prolactin levels are involved in the reduction of feed intake.

Prolactin has been reported to act as an immunomodulator (Hiestand et al., 1986; Mukherjec et al., 1990; O'Neal and Yu-Lee, 1991; Yu-Lee et al., 1991). A recent report by Gay et al. (1990) indicated that mice and rats given a diet of E+ tall fescue seed exhibited impaired immune function. However, cattle did not show a similar response. Other effects of prolactin in mammals include synergistic effects with steroid hormones on male and female gonads, water and electrolyte balance, effects on male sex accessory glands (conditioning effect), and temperature regulation (Nicoll and Bryant, 1972; Faichney and Barry, 1986).

Although prolactin is necessary to initiate lactogenesis, the involvement of progesterone and estrogen in lactation is significant. Estrogen and progesterone stimulate development of ductal and secretory structures when mammary tissue is primed with insulin, aldosterone, and prolactin (Forsyth, 1983). Estrogen is necessary for the cell division in terminal end buds that leads to ductal growth, and progesterone stimulates lobulo-alveolar growth. Prolactin is necessary to prime mammary tissue and apparently acts synergistically with estrogen and progesterone to promote mammary tissue growth (Forsyth, 1983). Mammary development in the horse begins 2 to 6 wk before parturition (Evans, 1990), but Worthy et al. (1986) have shown that the large increase in prolactin levels occurs only 5 to 10 d before parturition. Progesterone levels in normal gravid mares rise during the last 30 to 40 d of gestation and estrogen levels decrease (Pashen, 1984). Research by Redmond et al. (1993), Redmond (1994), and Taylor (1993) show opposite patterns for prolactin, progesterone and estradiol-17 β (Figures 2, 3, and 4). Mares grazing E+ pastures have lower serum progesterone and prolactin and higher estradiol-17 β than normal mares during the latter stages of gestation. The alteration in the levels of these hormones in gravid mares grazing E+ pastures and their interaction in mammary tissue development and subsequent lactation is significant in explaining the agalactia seen in these mares.

3.2. Progesterone

Progesterone is an extremely important hormone for the maintenance of pregnancy. It is fundamental for the provision of uterine secretions in preparation for the implantation of the embryo (Breudehmuehl et al., 1994; Hafez, 1987). It is also necessary for embryo motility, fixation and orientation within the uterus. Alterations in normal levels of progesterone could affect embryo motility and hinder maternal recognition of

pregnancy resulting in early embryonic loss (Breudehmuehl et al., 1994). In the normal mare, progesterone levels rise in early pregnancy, originating from the primary corpus luteum and later form accessory corpus lutea. Growth of the accessory corpus lutea are supported by follicle stimulating hormone (FSH) and equine chorionic gonadotrophin (ECG) which is released from the endometrial cups.

Holtan et al. (1991) found that progesterone concentrations in the mare were highest around day 100 of pregnancy. Progesterone was not detectable during mid-to late-gestation and ranged from undetectable to 1 ng/ml 5 days prior to parturition. According to a review by Vivrette (1994), an increase in the reduced pregnanes, primarily 20 α -hydroxy-5 α -pregnon-3-one (20 α -5p) and 5 α -pregnone-3 β , 20 α -diol was first detected in pony mares between 30 and 60 days of gestation. Increase in these reduced progesterone metabolites at this time suggests that they were produced by the fetoplacental unit. Also, according to Vivrette, their concentrations gradually increase during mid and late gestation and then rapidly increase 30 days prepartum. Maximum concentrations of 20 α -5P and 20-diols were observed during the last 2 to 3 days of pregnancy; this was followed by a decline before parturition. Pashen (1984) has suggested that the reduced progestogens compete with progesterone for binding sites in the myometrium, thereby causing a decrease in progesterone inhibition of myometrial activity.

Mares grazing endophyte infected tall fescue exhibit reduced levels of serum progestogens and its metabolites (Schmidt and Osborn, 1993; Monroe et al., 1988; Sharp and Bazer, 1995; Redmond et al., 1993). Although the mechanism by which progestogens are altered has not been elucidated, researchers believe it may have to do with altered progesterone metabolism by the placenta. This alteration is thought to be under the control of fetal cortisol levels (Pashen, 1994), which may be affected by the presence of *Neotyphodium coenophialum* toxins (Labrie et al., 1983).

3.3. Estradiol-17 β

Estrogen is another hormone that is important in the maintenance of pregnancy. In the normal mare, peak levels are achieved during the seventh and eighth months of gestation and gradually decrease as parturition nears (Pashen, 1984). This rise and fall in estrogen level coincides with the growth and subsequent regression of the fetal gonads. It is thought that the fetal gonads produce androgen precursors, such as dehydroepiandrosterone (DHA), which circulate through the placenta where they are aromatized to estrogens (Vivrette, 1994). Because of this, a correctly functioning fetoplacental unit is crucial in the proper production of estrogens. Estrogens are also important for mammary duct growth (Cross et al. 1995), and can influence blood flow and distribution in the uterus of sheep (Pashen, 1984). When parturition nears, estrogens stimulate prostaglandin production and oxytocin receptor synthesis in the uterus (Vivrette, 1994).

Consumption of E+ tall fescue has been shown to elevate estradiol-17 β levels in gravid mares (Redmond et al., 1994; Redmond et al., 1993; Taylor, 1993; Altom, 1994). According to Luthy and Calandra, bromocriptine, a dopamine agonist similar to that in E+ fescue, inhibited the binding of estrogen to its receptors in the adrenal gland of rats and caused a subsequent dose dependent increase in plasma estrogen. High doses of bromocriptine were also found to inhibit estrogen from binding to its receptors in the rat uterus. The inhibition of estrogen binding and subsequent force of estrogen into circulation would agree with the above findings and could be an explanation for the increased estradiol 17 β levels seen in mares grazing E+ fescue. If estrogen does direct blood flow to the placenta in horses as it does in sheep, the inability of estrogen to bind to its receptors might allow the misdirection of nutrients carried by the blood to the fetus and could result in dysmature foals (Pashen, 1979). Also, without the opportunity to bind to its receptors, estrogens might not be able to properly stimulate prostaglandin and oxytocin receptor synthesis, thereby resulting in prolonged gestation.

3.4. Cortisol

Reports on equine cortisol levels have been somewhat variable and the exact role cortisol plays in parturition is not clear. Nathanielsz et al. (1975) found maternal cortisol levels to be fairly constant when measured periodically from day 227 to day 324 of gestation. Lovell et al. (1975) found 11 β hydroxycorticosteroid in the mare to be unchanged during the prepartum period. According to Vivrette (1994), maternal cortisol levels increase three-fold on the day before foaling and five-fold during second stage labor as compared to levels observed during late gestation. There does not seem to be much placental transfer of cortisol in either direction (Nathanielsz et al., 1975). Of greater importance than maternal cortisol levels are fetal cortisol levels. Pashen (1984) and others (Vivrette, 1994; Sharp and Bazer, 1995) have hypothesized concerning the corticotrophin releasing hormone (CRH)-induced rise in fetal cortisol levels which is thought to trigger a chain of events ultimately ending in parturition. Chavette et al., 1993 indicated that 30-40 ng/ml is a critical level at which certain progestogens can stimulate estrogen and

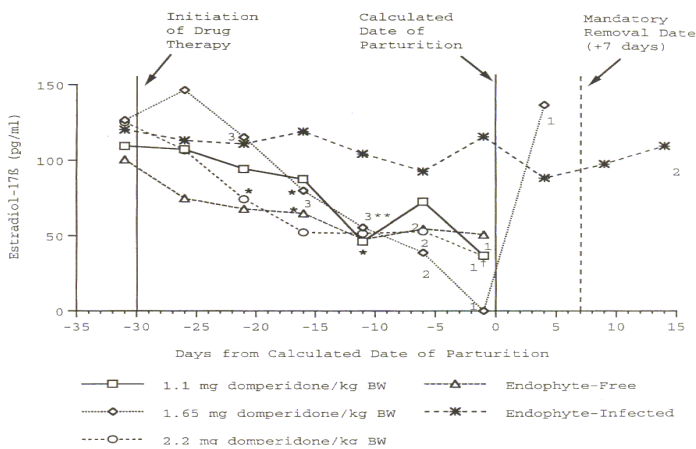


Figure 4. Effect of endophyte-infected fescue and domperidone treatment on serum estradiol-17 β levels in gravid mares. First detectable differences ($P < .05$) from pre-treatment levels are indicated by stars. Unless otherwise indicated, data points represent four mares per treatment (dagger indicates number of mares in endophyte-free group; double asterisk represents number of mares in 1.65 and 2.2 mg domperidone/kg BW groups). Mares which were not prepared for parturition seven days after the calculated date of parturition (as determined by veterinary examination) were relocated to endophyte-free pasture (from Redmond, 1994).

prostaglandin production to trigger uterine contractions. However, Nathanielsz et al. (1975) did not find cortisol concentrations that high. This may be due to the time period in which the samples were taken. Normally, fetal cortisol levels should begin to rise between 96 and 72 hours before parturition in response to increased adrenocorticotrophic hormone (ACTH). They should peak 30-60 minutes after birth (Nathanielsz et al., 1975; Sharp and Bozar, 1995). Based on available evidence, the foal probably has increased adrenal activity before parturition but there does not seem to be a dramatic increase as is seen in the lamb (Nathanielsz et al., 1975).

Brendemuehl et al. (1994) found decreased cortisol levels in foals born to mares grazing E+ fescue. Apparently, these foals did not show increased cortisol levels and the hypothesized chain of events leading to parturition did not occur. In the dams of these foals, it seems that parturition was initiated independently of fetal adrenal activity or cortisol levels. Additionally, foals in this study that survived the natal period showed increased cortisol levels during the first day of life. Increased cortisol concentrations are an indicator of the adrenal gland's ability to properly handle the stress of the postnatal period (Pashen, 1984). Foals in the above study that did not survive the first 24 hours did not show an increase in cortisol concentrations.

Rossdale et al. (1992) injected ACTH into pony fetuses between 245 and 321 days of gestation and observed a rise in maternal progesterone. It is possible that the preparturient rise of plasma progesterone concentrations in the mare prior to parturition could be a result of fetal adrenocortical activity. Since the adrenal gland of fetuses of E+ mares appear to be compromised, one might expect lower circulating total progesterone levels in the mare. As mentioned previously, low circulating levels of total progesterone have been well documented in mares consuming E+ fescue.

3.5. Thyroid Hormones

Recently, researchers have been studying the possible abnormalities of foal organs when their dams grazed E+ fescue during gestation. According to complete histopathologic studies of foal organs, only the thyroid gland showed abnormalities. In foals that had been exposed to the endophyte throughout gestation or from day 300 through parturition, distended, colloid-filled follicles were found in the thyroid gland. These colloid-filled follicles were larger than those found in foals that had not been exposed E+ fescue. Additionally, triiodothyronine (T₃) concentrations were lower in foals exposed to the endophyte (Boosinger et al., 1995; Breudemuehl, 1995; Sharp and Bazer, 1995). According to Boosinger, these distended follicles suggest colloid goiter. The reduced T₃ concentrations may indicate a hypothyroid condition even though the thyroid gland was not found to be extremely enlarged. Although the exact cause for hypothyroidism in foals is not known, the condition is probably associated with the incoordination, poor suckle reflex, hypothermia, and goiter seen in E+ foals. Musculoskeletal disorders such as tendon contracture and delayed bone development have also been reported (Boosinger

et al., 1995). Another manifestation of hypothyroidism is abortion or birth of weak young (Frandsen and Spurgeon, 1992).

Strickland et al. (1994) reported that the ergot alkaloids present in endophyte infected fescue are capable of binding to the D2 class of dopamine receptor on the pituitary lactotroph cells of rats and inhibiting prolactin release. Furthermore, Labrie et al. (1983) found that ergot alkaloids inhibited CRH-induced ACTH secretion by binding to the D2 class of dopamine receptor in the corticotroph cells of the autenion pituitary of rats and cattle. It is possible that these alkaloids could also inhibit or reduce the release of thyroid stimulating hormone (TSH) from the fetal pituitary thereby altering T₃ and thyroxine (T) concentrations (Breudemuehl et al., 1994). Clearly, more research needs to be done to elucidate the role of the thyroid hormones on the viability of postdate foals.

3.6. The Fetal Hypothalamic-Pituitary-Adrenal Axis (HPA) and Equine *Neotyphodium Coenophialum* Toxicosis

From the previous discussions, it is apparent that the endocrine system of the mare and foal is greatly altered when E+ fescue is consumed. The effects of E+ fescue on fetal development and the endocrine system of the mare and foal provide an excellent model for the study of the factors involved in normal fetal development and normal parturition and lactation in the mare.

Collectively, the preceding discussions of the endocrinology of the mare and foal leads one to suspect certain systems have gone awry to cause the various effects observed. Combining these data with what is known about normal parturition and fetal development leads this author to suspect the fetal HPA as a major player.

Challis et al. (1993) summarized the numerous endocrine factors involved in normal birth with much of the information drawn from studies with sheep. Birth appears to be effected through sequential maturation of the fetal HPA and the resulting increase in cortisol. Adrenocorticotrophin (ACTH) secretion is affected by corticotrophin releasing hormone (CRH), arginine, vasopressin, prostaglandin E, (PG) and endogenous opioids. According to these authors, fetal adrenal activation results form an increase in ACTH receptors and enhanced coupling through the G, protein to adenylate cyclase and increased expression of key steroidogenic enzymes including P450_{C17}. Cortisol modulates the mechanism by which ACTH activates fetal adrenal function, through specific glucocorticoid receptors in the fetal adrenal cortex. Cortisol also stimulates an increase in the concentration of its own high affinity binding protein in the fetal circulation.

Brendemuehl et al. (1994) reported decreased plasma levels of ACTH and cortisol in newborn foals from mares consuming E+ tall fescue. Ergot alkaloids have been shown to block CRH stimulated adenylate cyclase activity in rat pars intermedia cells in vitro (Labrie et al., 1983). Since CRH affects ACTH release from anterior pituitary cells via a cyclic adenosine monophosphate (c-AMP)-dependent mechanism (Giguere et al., 1982) and subsequently adrenal cortisol release, it is highly possible that the ergot alkaloids of E+ fescue effect an increase in gestation length in E+ mares by

blocking CRH effects on adenylate cyclase in the pars intermedia cells of the fetus. Without the increased fetal cortisol levels, the proper signals to the mare would not occur in fetuses of E+ mares. This would delay parturition and many of the processes involved in normal preparation for parturition.

Hypothyroidism in the newborn infant is associated with incoordination, poor suckle reflex, hypothermia, and goiter. The findings that the thyroid of E+ foals contained colloid-filled follicles and that triiodothyronine (T₃) levels were lower in foal plasma could help to explain the uncoordinated and weakened appearance of newborn E+ foals.

The highly depressed plasma prolactin and progesterone and elevated estradiol levels in E+ mares, all of which are involved in mammary tissue development and lactation, is surely related to the agalactia seen in these mares.

4. MANAGEMENT AND TREATMENT OF NEOTYPHODIUM COENOPHIALUM TOXICOSIS

4.1. Pasture Management

Horses and other non-ruminants appear to be much more sensitive to E+ fescue than ruminants. Unlike ruminants, the horse does not benefit from pre-gastric metabolism of alkaloids (Nacheuheim et al., 1992) and would be subject to absorption of a larger quantity of the unaltered alkaloids that were consumed. Personal interviews of horse owners and veterinarians has revealed that many horses exhibit many of the symptoms of E+ fescue toxicosis while consuming only small quantities in hay, small patches of E+ fescue hay in paddocks or even by grazing a small quantity of E+ fescue under paddock fences. Therefore, pastures must be completely riddened of E+ fescue to prevent toxicosis in horses. Personal experience and interviews with livestock owners throughout the U.S. attest to the extreme difficulty of ridding pastures of E+ fescue. Experience has shown that unless pastures are completely devoid of E+ plants and viable seed, the E+ plants begin to thrive and become significant problems within one to three years after re-planting of pastures. Best success with pasture re-seeding has come through the use of chemical killing of the fescue sword followed by aggressive choke crops for two years before re-seeding is attempted. Establishment of clover or other forage mixes with E+ fescue seems to be a reasonable alternative for cattle, but not for horses.

4.2. Grazing Behavior

The horse is a notorious selective grazer and will select many alternative forage species before consuming E+ fescue. Under low grazing pressures, many mares will spot graze other species of forage and never exhibit any signs of fescue toxicosis. Changes in grazing pressure or availability of alternative forages can quickly force E+ fescue consumption and the classical signs of fescue toxicosis. This explains why some horse owners appear to have little or no fescue toxicosis when a few mares are grazing a large acreage of mostly E+ fescue, and other horse owners routinely have problems.

4.3. Removal of Mares from E+ Pastures

There is evidence to suggest that mares need to be withdrawn from E+ pastures at least 30 days prior to expected foaling (Taylor, 1993). Brendemuehl et al. (1995) arrived at similar conclusions. Most veterinarians recommend removal of mares from E+ pastures from 30 and up to 90 days prior to expected foaling. From personal contact by this author with veterinarians and horse owners, it is apparent that even with long term removal from E+ pastures, some mares develop the classical signs of fescue toxicosis though usually not as severe. If the farm has fescue on it, there remains the potential for fescue contamination of hay and for limited consumption of fescue under paddock fences and small amounts in paddock areas.

4.4. Therapeutic Treatment

4.4.1. Selenium. Early studies with horses indicated that administration of selenium might alleviate the effects of E+ tall fescue on pregnant mares (Heimann et al., 1981). However, a subsequent study by Taylor et al. (1985) found that selenium had no effect. Also, Monroe et al. (1988) injected mares on E- and E+ tall fescue pasture with selenium intramuscularly (2.5 mg/kg body weight) at 28-d intervals. The results confirmed the findings of Taylor et al. (1985) that there were no beneficial effects in relieving the signs of tall fescue toxicosis attributed to selenium therapy.

4.4.2. Dilution of Toxin Intake. Gravid mares were fed 50% of the NRC requirement for energy as cracked corn for the last 90 d of gestation (Earle et al., 1990). There were no beneficial effects as a result of grain feeding. Foal mortality was 66 and 100% for the energy and no energy supplement treatments, respectively. Mare mortality was 66 and 50% for the energy and no energy supplement treatments, respectively. This study also confirmed the severity of the problems under the conditions in the Southeastern USA.

4.4.3. Phenothiazine. Phenothiazine was administered orally (2 g mare⁻¹ day⁻¹) for 40 d before expected foaling date (Redmond et al., 1991a). Phenothiazine was ineffective in relieving any of the signs associated with tall fescue toxicosis in gravid mares.

4.4.4. Evidence of Dopamine Receptor Involvement. The consistent observation of decreased serum prolactin levels in animals receiving diets of E+ tall fescue (Porter et al., 1985; Bond and Bolt, 1986; Elsasser and Bolt, 1987; Evans et al., 1988; Monroe et al., 1988; Redmond et al., 1991a; Redmond et al., 1991b) indicates the involvement of dopamine receptors in tall fescue toxicosis. This conclusion, based on reduced serum prolactin levels, is derived from dopamine's involvement in the control of prolactin secretion in vivo. Also, several recent studies provide further evidence of dopamine receptor involvement in tall fescue toxicosis. Strickland et al. (1992) used isolated pituitary cell preparations and provided evidence that the alkaloids of tall fescue serve as dopamine agonists to effect a reduction in prolactin production from the lactotroph cells. Ireland et al. (1991) demonstrated that the selective dopamine agonist bromocriptine (Fluckiger, 1975) could cause signs of equine fescue toxicosis. Redmond et al. (1992) demonstrated that a selective D2 dopamine

receptor antagonist, domperidone (Stoof and Keabian, 1984), was capable of eliminating the signs of equine tall fescue toxicosis. Kitzman et al. (1986) and Lipham et al. (1989) also reported that a dopamine antagonist, metoclopramide, reversed signs of tall fescue toxicosis in cattle. These studies strongly support the involvement of dopaminergic mechanism in tall fescue toxicosis.

4.4.5. Dopamine Receptors, Locations, and Action. Five different subclasses of the dopamine receptor have been identified on the basis of biochemical, molecular, and pharmacological properties. The sub classes are D1 and D2 (Keabian and Calne, 1979), D3 (Sokoloff et al., 1990), D4 (Van Tol et al., 1991), and D5 (Sunahara et al., 1991). Dopamine receptors are dispersed throughout the body and seem to affect the function of several tissues (Hosgood, 1990). Tissues listed as having D1 and D2 dopamine receptors include renal and mesenteric vascular smooth muscle (vasodilatory effect, D1 receptor), the striatum (inhibit acetylcholine and dopamine release, D2 receptor), bovine parathyroid gland (increase parathyroid hormone release, D1 receptor), carotid body (depression of chemosensory activity, D2 receptor), sympathetic nerve terminals (inhibit norepinephrine release, D2 receptor), and the anterior and intermediate lobes of the pituitary gland (prolactin and α -melanocyte-stimulating hormone, D2 receptor), as well as others (Cooper et al., 1991). The D3, D4, and D5 receptors have only recently been identified, therefore, studies of the biochemical and pharmacological activities of these receptors are just beginning. Some of the aforementioned receptor activities listed for the D1 and D2 receptor subtypes may actually be mediated through these newly-discovered dopamine receptor subtypes. It should also be noted that the pharmacological activity of the ergot alkaloid group of tall fescue toxins are different for the D1 and D2 receptors. These alkaloids interact with the D2 receptor in an agonistic fashion, whereas interaction with the D1 dopamine receptor is in an antagonistic fashion (Siegel et al., 1989).

Again, reduction in prolactin secretion is most likely caused by agonistic interaction of tall fescue toxins with the D2 receptor on the lactotroph. As previously mentioned, feed intake seems to be reduced when animals consume tall fescue toxins. Feed intake may be affected by toxin interaction with dopaminergic mechanisms. Several reports indicate that dopamine is capable of modifying gut motility (Sorraing et al., 1984; King and Gerring, 1988; Stafford and Leek, 1988; Clark and Moore, 1989). Likewise, dopamine is known to stimulate the feeding center of the hypothalamus (Newsholme and Leech, 1983) and have effects on mesenteric blood vessels (Gilman et al., 1990). Therefore, compounds interacting with dopamine receptors, such as the ergot alkaloids, may affect gut motility, gut perfusion, and digestion kinetics; thus possibly altering nutrient availability as well as feed intake. The distribution and wide range of physiological activities of the dopamine receptors suggest that these receptors should receive more attention in the future as sites of action for the tall fescue toxins.

4.4.6. Dopamine Antagonists. Although not present in

tall fescue, bromocriptine is an ergot alkaloid and a dopamine receptor agonist. Ireland et al. (1991) administered bromocriptine to gravid pony mares and observed signs that were similar to those seen in mares grazing E+ tall fescue. Administration of perphenazine, a dopamine receptor antagonist and a phenothiazine derivative, provided some relief in the signs seen with bromocriptine administration. In non-pregnant pony mares, administration of perphenazine at 1.0 mg/kg body weight increased plasma prolactin, but resulted in hyperesthesia (Loch et al., 1990). Metoclopramide has been used to increase plasma prolactin levels and decrease body temperature in calves grazing E+ pasture (Lipham et al., 1989). In rats, fluphenazine and trifluoperazine had mammatrophic effects (Ben-David et al., 1965). Other drugs such as chlorpromazine and acepromazine have some potential for dopamine antagonist activity, but all of the aforementioned drugs can have considerable neuroleptic activity because all cross the blood-brain barrier and have central nervous system effects. The potential for secondary neuroleptic effects negates these drugs from serious consideration as treatments for tall fescue toxicosis.

Strickland et al. (1994), studied the effects of ergot and loline alkaloids of E+ fescue on prolactin release by isolated and perfused rat pituitary cells. The ergot alkaloids had prolactin lowering effects. The use of a D2 dopamine receptor antagonist (domperidone) blocked the effect of the ergot alkaloids and prevented their prolactin lowering effect. Domperidone is a D2 dopamine receptor blocker that does not cross the blood brain barrier and elicit neuroleptic side effects. Domperidone was administered orally (1.1 mg/kg body weight) to gravid mares grazing E+ tall fescue (Figures 2, 3, and 4). Domperidone increased serum prolactin and progesterone and provided what seemed to be nearly complete recovery of gravid mares from tall fescue toxicosis without side effects of the drug. Treated mares had milk, live, healthy foals, and gestation length similar to the calculated gestation length. Subsequently, a dose titration study was conducted to determine the minimum effective dose of domperidone for treating tall fescue toxicosis (Redmond et al. (1993). Again, domperidone provided recovery from tall fescue toxicosis in gravid mares and the minimum effective oral dose was 1.1 mg/kg body weight when administered daily for 30 d before foaling. Also, to provide additional data for U. S. Food and Drug Administration approval of domperidone for treatment of equine fescue toxicosis, we have conducted an additional dose titration study (Campbell et al., 1996) and a short duration dosing study (Dooley et al., 1996). As a part of clinical testing data requirements, we have treated several hundred mares throughout the fescue growing regions of the U.S. Domperidone has proven to be a highly effective treatment for equine fescue toxicosis without neuroleptic side effects. Our current recommendations for mares that are to remain on E+ fescue up to foaling are to administer the drug orally once daily starting 15 days prior to expected foaling date and continuing up to foaling. For mares that are removed from E+ pastures but aren't exhibiting proper udder development, we recommend starting the drug 10 days prior to expected foaling and continuing to foaling. For mares that

foal and are agalactic or have a low level of milk production, the drug is started at foaling and continued for at least five days or until lactation is initiated. If the drug is started several days after foaling, more doses may be required to initiate a suitable lactation. Also, we have treated several agalactic or low milk producing mares in which the lactation problems were not associated with fescue toxins. Domperidone has been effective in rectifying lactation problems in a high percentage of these mares.

4.4.7 Mechanism of Action of Domperidone for Treating Equine Fescue Toxicosis Domperidone's action as a D2 dopamine receptor blocker prevents the ergot alkaloids from mimicking dopamine actions. The most apparent action of dopamine and the ergo alkaloids of fescue is their prolactin lowering effect. With administration of domperidone to E+ mares, prolactin is returned to normal levels and even increased above normal level: in most instances (Redmond et al., 1993). Certainly prolactin is a major player in equine fescue toxicosis but as is evidenced by the preceding review of endocrine effects of E+ fescue, prolactin is one of many hormones altered. Prolactin, along with the progesterone and estrogen are certainly major players in the milk production maladies observed in E+ mares and administration of domperidone returns these hormone levels to near normal levels.

Since the HPA of the fetus in E+ mares appears to be compromised and results in prolonged gestation in mares and the associated problems thereof, domperidone may be having some effect on the HPA system since mares receiving domperidone while grazing E+ fescue foal at or near their expected foaling date with normal, healthy foals. Since ACTH levels in foals from E+ mares are low, and ACTH is the stimulus for adrenal cortisol release and since normal fetal adrenal cortisol levels appear to be necessary to trigger parturition, it is interesting to speculate that domperidone may be affecting this system. Zerbe et al. (1993) administered domperidone to dogs and observed an enhanced ACT response to CRH injections. Thus, domperidone could be reversing the effects of E+ fescue on gestation length by effecting an increase in adrenal cortisol through CRH stimulated release of ACTH. Direct evidence to confirm this theory does not exist.

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